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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/722,659	09/27/96	BENNETT D	104385.140

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EXAMINER	
LUBET,M	
ART UNIT	**PAPER NUMBER**
1644	19

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
08/722,659	Bennett et al.
Examiner	**Group Art Unit**
Lubet	1644

☒ Responsive to communication(s) filed on *January. 15, 1999*.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-7* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-7* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *18*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

1. The request filed on January 22, 1999 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 08/722,659 is acceptable and a CPA has been established. An action on the CPA follows.

2. This office action is in response to Paper 15 filed January 22, 1999.

3. Claims 1-7 are under examination.

4. The text of those section of Title 35, U.S.C. not included in this action can be found in a prior office action.

5. Applicant request for an interview with the Examiner is acknowledged. In a telephone interview, on June 6, 1999, Examiner Lubet and Applicant's representative, Gretchen Rice, discussed this application. If Applicant wishes to further discuss this application with Examiner Lubet, Applicant's representative should telephone Examiner Lubet to arrange an interview.

6. As noted in Paper 16 mailed June 3, 1999, Applicant's petition to accept the declaration filed under 35 USC 1.131 was granted. Accordingly the petition has been considered (see below).

Rejections under 35 USC 112, second paragraph

7. Claim 6 stands rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. (maintained) The term "overexpressed " in claim 6 is a relative term which renders the claim indefinite. The term "overexpressed" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The metes and bounds of the term are unclear.

--Applicant has not addressed this issue in Paper 15.

Rejections under 35 USC 112,first paragraph

8. (maintained) Claims 1-7 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method to decrease inflammatory response in ischemic tissue by administering Heparanase III, does not reasonably provide enablement for numerous inflammatory diseases or conditions disclosed on page 1, lines 25-35 or treatment of inflammation with other heparinases (IE heparinase II). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Reasons are set forth below

A. The effectiveness of treating inflammatory conditions such as organ transplantation, allograft rejection, rheumatoid arthritis, asthma, rhinitis and glomerulonephritis by administering heparinase *in vivo* is unknown.

Pharmaceutical therapies are unpredictable for the following reasons: (1) the peptide(s) or protein may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to inherently short half-life of the peptide or protein; (2) the peptide(s) or protein may not reach the target area, i.e. the peptide(s) or protein may not be not be able to cross the mucosa or may be adsorbed by fluids, cells and tissues where the peptide(s) or protein has no effect, (3) other functional properties, known or unknown, may make the protein unsuitable for *in vivo* therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO BD. APP. & Inter. 1992).

Burnham(AM. J. Hospt Pharm 51: 210, 1994) teach that use of therapeutic proteins is unpredictable because the proteins have poor stability and short half-lives *in vivo* and their repeated use leads to immunogenic response, leading to a vicious cycle of raising the dose, which enhances the immune reaction which increases clearance.

Custoldi et al. (Agents Actions 42:40, 1994) teach that administration of some anti-inflammatory drugs, such as protamine, is effective if administer locally but is not effective if administered systemically (see page 41, right , last paragraph, in particular). Therefore it is unpredictable that administration of heparinase systemically will be effective in decreasing localized inflammatory responses.

The inflammatory process is a complex, multifaceted process involving a myriad of tissue products including histamine, bradykinin serotonin, prostaglandin, reaction products of the complement system and lymphokines and multiple mechanisms (see Guyon , 1991 and Cotran et al., 1991).Inflammatory responses encompass acute inflammation and chronic inflammation (see Cotran et al.). The specification discloses that heparinase II decreases inflammatory responses in response to ischemia, but does teach that heparinase will be effective in treating other

inflammatory responses. For instance, one with skill in the art would doubt that heparinase could decrease the release of histamine or prostaglandins. Sasisekharan et al US 5, 567, 417 Patent discloses that Heparinases I and III inhibits both neovascularization *in vivo* and proliferation of capillary endothelial cells mediated by fibroblast growth factor in vitro. The '417 Patent also teaches that Heparinase II did not inhibit neovascularization *in vivo*, but is useful in the alteration of smooth muscle cell proliferation (see column 3, line 33 through column 4, line 39, in particular). Thus species of heparinase (IE enzymes that cleave glycosidic linkages in heparin and heparan sulfate) have different in vivo effects. Absent data to demonstrate that a particular heparinase can decrease a particular inflammatory response in vivo, one with skill in the art would not predict that a particular heparinase would decrease a particular inflammatory response.

Therefore, in view of the nature of the invention, the state of the art, the amount of guidance present in the specification, and the breath of the claims, it would take undue experimentation to practice the claimed invention

-- Applicant's response on pages 2-4 of Paper 15 has been considered but is not persuasive. There is no data to indicate that the administration of heparinase enzymes is effective in treating chronic diseases such as arthritis, asthma, rhinitis and glomerulonephritis. Applicant urges that all inflammation is controlled by chemokines and that all chemokines are bound to the cell surface by heparin and heparan sulfate. Applicant points to Figure 2 of Luster et al. as support for this allegation. However, Luster et al. does not teach that all cytokines bind to heparin. Heparin and heparin sulfate bind a variety of molecules, including molecules such as protamine which may downregulate the inflammatory response (see Yayon et al. US 5789182 Column 1, lines 50-55 and Castoldi et al., abstract and page 42, in particular). Depletion of a localized area by treatment with heparinase may also deplete the area of molecules that contribute to the downregualtion of inflammation. The claim language encompasses treating localized inflammatory responses that may result from chronic diseases such as the ones cited above.

Applicant's argument that one of ordinary skill in the art at the time of the invention would expect that the removal of chemokines whether they are chemokines that are present due to ischemia or "other cheomkines" by digestion of heparan sulfate and heparin with heparinase enzyme would result in the decrease of a localized inflammatory response regardless of which chemokine and infiltrating cells are specifically responsible for the inflammation at that site is not supported by factual evidence. There is no evidence of record that indicates that the ability to decreased inflammation caused by ischemia is predictive of ability to treat inflammation that results from other mechanism, IE bacterial infection, allergic reactions, etc.

Rejections under 35 USC 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.
> (f) he did not himself invent the subject matter sought to be patented.

Claims 1-7 are rejected under 35 USC 102(e) or (f) over Zimmerman US 5,997,863 filed July 8, 1994. The inventive entity of Zimmerman et al. US 5,996,863 has inventors in common with the instant application but is not the same inventive entity as that of the instant application. The applied reference has a common inventor with the instant application. Based upon the earlier effective US filing date of the reference, it constitutes prior art under 35 USC 102(e). This rejection under 35 USC 102(e) might be overcome either by showing under 37 CFR 1.132 that any invention of this invention disclosed but not claim in the reference was derived from the inventor of this application and is thus not the invention "by another" or an appropriate showing under CFR 1.131.

Zimmerman et al. teach a method of treating ischemia in a rabbit hind limb ischemic model by administering heparinase 1 (see column 8, line 62 through claim 18, line 34, in particular). Zimmerman et al. also discloses that administering heparinase releases heparin binding growth factors and degrading components of the extracellular matrix, thereby facilitating the mobility of cytokines, chemoattractants and cells (see column 6, lines 25-59, in particular).

Zimmerman et al. also discloses that wound healing is generally divided into three temporally overlapping phases, inflammation, proliferation and remodeling. During inflammation, blood borne cells infiltrate the wound site and release mediating factors (see column 2, lines 56-67, in particular).

The instant specification on page 39 teaches that ischemia induces inflammatory responses such as migration of neutrophils across the connective tissue, extravasation of plasma and other blood and cellular components .

Therefore the method of treating ischemia by administering heparinase taught by Zimmerman et al. would also decrease the localized inflammatory responses that result from ischemia. Thus the methods of Zimmerman anticipate the instantly claimed method of decreasing localized inflammatory responses.

Rejections under 35 USC 103, second paragraph

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 1-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over. Hoogewerf et al. (W) (J. Biol. Chem 270:3268, February, 1995) , Gilat et al. (X)(J. Exp. Med. 181:1929, May, 1995), Vlodavsky et al (AA) (Invasion Metastasis 12: 112, 1991), Zimmerman US 5, 169,722 (issued Dec. 8, 1992), Fuks et al. US Patent 5,362,641 (issued Nov. 8, 1994, filed March 7, 1991) and Sasisekharan et al. US Patent 5,567,417 (issued October 22, 1996 has priority to November 17, 1993) in view of Nash et al. (J. of Pharmacology and Experimental Therapeutics 274:1463, 1995), Lider et al. (Y)(PNAS 92:5037, May 1995), Ratner et al. (Invasion Metastasis 12:82, 1992) or Gilat et al (AA) (J. Immunol. 153:4899, 1994), The

claims are directed to methods of treating localized inflammatory responses by administering heparinase enzymes. Claim 6 recites a limitation wherein the heparinase enzyme is overexpressed from a recombinant nucleotide sequence in Flavobacterium heparinum. Claim 7 recites a limitation wherein the heparinase enzyme is expressed from a recombinant nucleotide sequence in an organism in which it does not naturally occur.

Hoogewerf et al. teach a pharmaceutical composition comprising heparinase enzyme obtained from human platelets (see abstract and page 3269, in particular).

Gilat et al. teach pharmaceutical composition comprising heparinase enzyme obtained from human placenta (see pages 1929-1930, in particular).

Vlodavsky et al. teach a heparinase enzyme, heparitinase. The heparitinase enzyme taught by Vlodavsky et al. is encompassed by the claim language since the specification discloses on page 14, lines 19-33 that heparinase enzyme is an enzyme that degrades heparin.

The Zimmerman '772 Patent discloses heparinase enzymes expressed by *Flavobacteruim heparinum* and a method of producing heparinase enzyme recombinantly in an organism in which it does not naturally occur (see column 3, line 26 through column 6, line 16, and column 8 line 4 through column 10 and claims 1-2, in particular).

The Fuks '641 patent discloses purified heparinase obtained from human SK-HEP-1 in a pharmaceutical composition (see column 12, line 59 through column 16, line 54 and claims 1-39, in particular). The '641 Patent further teaches that FGF is released by addition of heparinase to extracellular matrix (ECM) which promotes wound healing. Wound healing is a facet of inflammation. The '641 Patent also discloses but does not exemplify that administration of heparinase can be used to treat diseases or conditions such as transplantation, diabetes, hypertension, cerebral and peripheral ischemic disease, and diseases associated with vascular

damage, such as diabetes, hypertension and systemic lupus erythematosus (see column 4, line 38 through column 5, line 6, in particular).

The Sasisekharan '417 Patent discloses pharmaceutical compositions for delivering an effective dose of heparinase (see column 8, line 29 through column 11, line 7 and Claims 1 in particular). The '417 Patent also discloses that the heparinase may be administered in composition comprising biodegradable polymeric matrices or liposomes (see Claims 4 and 8, column 16, lines 17-27, in particular). The '417 Patent discloses three heparin enzymes produced by Flavobacterium heparinum. The '417 Patent further discloses that Heparinases I and III inhibits both neovascularization *in vivo* and proliferation of capillary endothelial cells mediated by fibroblast growth factor in vitro. The '417 Patent also teaches that Heparinase II did not inhibit neovascularization *in vivo*, but is useful in the alteration of smooth muscle cell proliferation (see column 3, line 33 through column 4, line 39, in particular). The '417 Patent further discloses but does not exemplify the use of heparinase to treat disease in which neovascularization plays a prominent role such as rheumatoid arthritis and eye diseases such as diabetic retinopathy, neovascular glaucoma, and inflammatory eye disease (see column 1, line 47 through column 2, line 25, in particular).

Hoogewerf et al., Gilat et al, , Vlodavsky et al. and the '772 Patent do not teach the use of the heparinase enzymes to treat inflammatory responses or that heparinase enzyme decreases accumulation of leukocytes or inhibits leukocyte extravasation. However, the limitations recited in Claims 2-5 are properties of the heparinase enzymes.

Nash et al. (J. of Pharmacology and Experimental Therapeutics 274:1463, 1995) teaches that angiogenesis is required for the progression of chronic inflammation and agents that alter it can affect the development of inflammation and the consequent tissue destruction (see abstract, in particular).

Lider et al teach that heparinase inhibits secretion of TNFα and that TNFα is a major mediator in T cell mediated inflammatory responses.

Ratner et al. teach that heparanases digests heparin and heparin sulfate from endothelial cell surfaces and facilitates T cell movement through the basement membranes (see page 82, in particular). Thus Ratner teaches that heparinase removes and digests heparin and heparan sulfate from endothelial cells as is claimed in claim 2.

Gilat et al.(AA) teach that heparanases degrades heparin from ECM which leads to the release of cytokines which leads to lymphocytes becoming mobile and migrating to adjacent sites of inflammation.

The '641 and '417 Patents disclose but do not exemplify administration of heparanases to treat localized inflammatory responses in a variety of diseases including cerebral and peripheral ischemic disease, diabetes, systemic lupus, inflammatory eye disease and rheumatoid arthritis.

Therefore it would have been obvious to one with ordinary skill in the art at the time of the invention to locally administer heparinase enzymes taught by Hoogewerf et al., Gilat et al., Vlodavsky et al., and the '772 , the '641 and the '417 Patents with the expectation that inflammatory responses would be decreased as taught by the '641 and '417 Patents, Nash et al. and Lider et al. Based upon the teachings of Lider et al., one skill in the art would expect that administration of heparinase would result in decreased levels of TNF α which would result in a decrease in inflammatory process mediated by TNF α .

One with skill in the art would also expect that administration of heparinase would decrease chronic inflammation process since Nash et al. teach that angiogenesis (neovascularization) is required for progression of chronic inflammation and Sasisekharan '417 discloses that Heparinases I and III inhibits neovascularization *in vivo*. Therefore one with ordinary skill in the

art at the time of the invention would be motivated to administer heparinase I or III to sites of chronic inflammation with the expectation that angiogenesis would be inhibit the chronic inflammation would decreased.

One with ordinary skill in the art would be motivated to administer heparinase to treat inflammation responses associated with transplantation, diabetes, hypertension, cerebral and peripheral ischemic disease, and diseases associated with vascular damage, such as diabetes, hypertension and systemic lupus erythematosus because Fuks teaches but does not exemplify that administration of heparinase can be used to treat such diseases.

Page 1 of the specification discloses that an inflammatory response in local response to cellular injury that is marked by capillary dilation, leukocytic infiltration, redness, hear and pain. The specification on page 1 further discloses that inflammatory responses can include ischemia/reperfusion injury following myocardial infarction, shock, stroke, organ transplantation, allograft rejection, rheumatoid arthritis, asthma, allergic rhinitis and glomerulonephritis. Therefore based upon the teachings of Fuks et al. one with ordinary skill in the art would be motivated to administer heparinase to ameliorate inflammatory response that results from ischemic disease, transplantation, or stroke.

-- Applicant's response on pages 4-6 of paper 9 has been carefully considered but is not persuasive.

The advisory action issued Dec. 10, 1998 indicates that the declaration filed Nov. 23, 1998 is sufficient to establish that the invention was conceived and reduced to practice prior to publications of Gilat (1995), Gilat (1994), Hoogewerf et al and Lider. **However, upon further consideration this position is vacated.** The declaration filed Nov. 23, 1998 established that heparinase inhibits neutrophil migration in vitro. It does not establish that administration of heparinase in vivo inhibits localized inflammation. Inflammation is a complex, multifaceted process which involves many different cell types IE (macrophages, neutrophils, endothelial cells, lymphocytes) , angiogenesis, erythema and tissue healing (see Guyton. page 848-371) . The

ability of heparinase to inhibit neutrophil migration in vitro does not establish that administration of heparinase in vivo is effective in decreasing localized inflammatory responses.

Applicant's response that the teaching that administration of Fuks et al. that administration of heparinase is useful to promote neovascularization does not suggest that administration of heparinase enzyme would be useful to decease localized inflammation is not persuasive. Fuks et al. clearly teach that FGF is released by addition of heparinase to extracellular matrix (ECM) which promotes wound healing. The '641 Patent also discloses but does not exemplify that administration of heparinase can be used to treat diseases or conditions such as transplantation, diabetes, hypertension, cerebral and **peripheral ischemic disease**, and diseases associated with vascular damage, such as diabetes, hypertension and systemic lupus erythematosus (see column 4, line 38 through column 5, line 6, in particular. Therefore one with skill in the art at the time of the invention would be motivated to administration heparinase locally with the expectation that it would promote decrease inflammation and promote would healing.

Applicant argument that the '417 patent is in direct contradiction to the 'Fuks '641 patent since it teaches that heparinase enzymes are useful to inhibit angiogenesis. However, as discussed supra, inflammation is a complex, multifaceted process which takes places over a number of days and weeks. Nash et al. (J. of Pharmacology and Experimental Therapeutics 274:1463, 1995) teaches that angiogenesis is required for the progression of chronic inflammation and agents that alter it can affect the development of inflammation and the consequent tissue destruction (see abstract, in particular).

Page 1 of the specification defines an inflammatory response as a local response to cellular injury that is marked by capillary dilation, leukocytic infiltration, redness, heat and pain. Thus Applicant's definition of the inflammatory response encompasses inflammatory responses such as transplantation, diabetes, hypertension, cerebral and peripheral ischemic disease, and diseases associated with vascular damage, such as diabetes, hypertension and systemic lupus erythematosus Fuks clearly teaches that administration of heparinase causes the release of

angiogenic endothelial cell growth factor such as FGF and that addition of heparinase may provide an effective method to mobilize and activate FGF. Fuks et al. teaches that conditions which are likely to benefit from neovascularization promoted of FGF include transplantation, diabetes, hypertension, cerebral and **peripheral ischemic disease**, and diseases associated with vascular damage, such as diabetes, hypertension and systemic lupus erythematosus (see column 4, line 38 through column 5, line 6, in particular.

Applicant's argument that the references in combination do not teach the claimed invention is not persuasive. One with skill in the art would be motivated to administer heparinase to patients with the expectation that heparinase or inhibit TNF α secretion which would lead to a decrease in inflammation for the reasons taught by Lider et al. One with ordinary skill in the art would have been motivated to administer heparinase locally with the expectation that it would inhibit angiogenesis (neovascularization) which would inhibit chronic inflammation as taught by Nash et al.

Double Patenting rejection

12. Claims 1-7 are directed to an invention not patentably distinct from claim of commonly assigned 5,997,863 . Specifically, Claims 1-9 of 5,997,863 are drawn to methods of enhancing normal would healing by administering heparinase 2, heparinase 3, and heparinase from Flavobacterium HP206. Wound healing is a type of inflammatory response, since inflammatory cells, such as neutrophils, participate in wound healing and many of the "inflammatory cytokines" IE TNF-α are participate in wound healing. The specification of 5,997,863 discloses that would healing is generally divided into three temporally overlapping phases: inflammation, proliferation and remodeling (see column 2, lines 56-65, in particular).

Commonly assigned 5, 997,863 , discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue,

the assignee is required under 37 CFR 1.78(c) and 35 U.S.C. 132 to either show that the conflicting inventions were commonly owned at the time the invention in this application was made or to name the prior inventor of the conflicting subject matter. Failure to comply with this requirement will result in a holding of abandonment of the application.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g).

13 .The non-statutory double patenting rejection, whether of the obviousness-type or non-obviousness-type, is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent. *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); and *In re Goodman*, 29 USPQ2d 2010 (Fed. Cir. 1993).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(b) and (c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.78(d).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-7 are rejected under the judicially created doctrine of obvious- type double patenting over claims 1-10 of Zimmerman 5,997,863. The conflicting claims are not identical, they are not patentably distinct from each other. The claims of 5, 997,863 pertain to method of treating wounds by administering heparinase. Wound healing is a type of inflammatory response, since inflammatory cells, such as neutrophils, participate in wound healing and many of the

"inflammatory cytokines" IE TNF-α are participate in wound healing (see Guyton , 1991 and Cotran et al., 1991). The specification of 5,997,863 discloses that would healing is generally divided into three temporally overlapping phases: inflammation, proliferation and remodeling (see column 2, lines 56-65, in particular).

--The rejection is maintained. Applicants have requested that the rejection be held in abeyance until allowable subject matter is indicated in the instant application and in 08/273,109.

14. Examiner believes that all pertinent arguments have been addressed.

15. No claim is allowed. **THIS ACTION IS MADE NON-FINAL.**

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Martha Lubet in Art Unit 1644 whose telephone number is (703) 305-7148. The examiner can normally be reached on Monday through Friday from 8:15 AM to 4:45 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan, can be reached at (703) 305-3973 The FAX number for this group is (703) 305-3014 or 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Martha T. Lubet
Jan. 31, 1999

CHRISTINA Y. CHAN
SUPERVISORY PATENT EXAMINER
GROUP ~~1800~~ 1640